

WHAT IS CLAIMED IS:

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1. An isolated DNA comprising a nucleic acid selected from the group of:
(a) a nucleic acid comprising a nucleotide sequence coding for human MiRP1 set forth in SEQ ID NO:2 or its complement;
(b) a nucleic acid comprising a nucleotide sequence coding for rat MiRP1 set forth in SEQ ID NO:4 or its complement;
(c) a nucleic acid comprising a nucleotide sequence coding for human MiRP2 set forth in SEQ ID NO:6 or its complement;
(d) a nucleic acid comprising a nucleotide sequence coding for mouse MiRP2 set forth in SEQ ID NO:8 or its complement;
(e) a nucleic acid comprising a nucleotide sequence coding for human MiRP3 set forth in SEQ ID NO:10 or its complement;
(f) a nucleic acid comprising a nucleotide sequence coding for mouse MiRP3 set forth in SEQ ID NO:12 or its complement;
(g) a nucleic acid which hybridizes under stringent conditions with a nucleic acid of any one of (a)-(f) and
(h) a nucleic acid which has at least 90% identity with a nucleic acid of any one of (a)-(f).

2. An isolated DNA encoding a polypeptide of SEQ ID NO:2 comprising a mutation disclosed herein.

3. A nucleic acid probe which hybridizes specifically to the DNA of claim 2 under stringent hybridization conditions wherein said stringent hybridization conditions prevent said nucleic acid probe from hybridizing to DNA of SEQ ID NO:1.

4. A nucleic acid probe which hybridizes specifically to the DNA of claim 2 under stringent hybridization conditions wherein said stringent hybridization conditions prevent said nucleic acid probe from hybridizing to DNA of SEQ ID NO:3.

Sub A 5. An allele specific probe or primer which hybridizes to the DNA of claim 1 or an allelic variant thereof under stringent conditions.

6. The probe or primer of claim 5 that is 10-100 bases long.

Sub A4 5 7. The probe or primer of claim 6 that comprises at least ten contiguous bases from SEQ ID NO:2, 4, 6, 8, 10 or 12, or an allelic variant thereof, or the complement of any of these.

8. An allele specific probe or primer that hybridizes to a subsequence of SEQ ID NO:2 including the 22nd, 25th, 161st or 170th base, or to the corresponding subsequence in the complement of SEQ ID NO:2 or an allelic variant thereof, when maximally aligned with SEQ ID NO:2.

Sub A5 9. 9. A primer suitable for performing a single base extension reaction across a polymorphic site, which primer hybridizes to a subsequence of SEQ ID NO:2 or the complement thereof, which subsequence terminates at base immediately adjacent to and 5' from a base selected from the group consisting of 22, 25, 161 or 170.

10. 15 A method for diagnosing a polymorphism which causes long QT syndrome comprising hybridizing a probe of claim 3 to a patient's sample of DNA or RNA under stringent conditions which allow hybridization of said probe to nucleic acid comprising said polymorphism but prevent hybridization of said probe to a nucleic acid of SEQ ID NO:1 wherein the presence of a hybridization signal indicates the presence of said polymorphism.

11. 20 The method according to claim 10 wherein the patient's DNA or RNA has been amplified and said amplified DNA or RNA is hybridized.

12. 13. A method according to claim 11 wherein hybridization is performed *in situ*.

13. A method for diagnosing the presence of a polymorphism in human *KCNE2* which causes long QT syndrome wherein said method is performed by means which identify the presence of said polymorphism, wherein said polymorphism is one which results in the presence of

a KCNE2 polypeptide of SEQ ID NO:2 with an altered amino acid, said altered amino acid being selected from the group described herein.

14. The method of claim 13 wherein said means is selected from the group consisting of (a) using a single-stranded conformation polymorphism technique to assay for said polymorphism, (b) sequencing human KCNE2 and (c) performing an RNase assay.

15. An antibody which binds to a mutant KCNE2 polypeptide but not to wild-type KCNE2 polypeptide, wherein said mutant KCNE2 polypeptide has the amino acid sequence of SEQ ID NO:2 with an altered sequence as disclosed herein.

16. A method for diagnosing long QT syndrome said method consisting of an assay for the presence of mutant KCNE2 polypeptide in a patient by reacting a patient's sample with an antibody of claim 15 wherein the presence of a positive reaction is indicative of long QT syndrome.

17. The method of claim 16 wherein said antibody is a monoclonal antibody.

18. The method of claim 17 wherein said assay is selected from the group consisting of immunoblotting and an immunocytochemical technique.

19. An isolated polypeptide selected from the group consisting of:

(a) a polypeptide comprising an amino acid sequence set forth in SEQ ID NO:2;

(b) a polypeptide comprising an amino acid sequence set forth in SEQ ID NO:2 with a mutation described herein;

(c) a polypeptide comprising an amino acid sequence set forth in SEQ ID NO:4;

(d) a polypeptide comprising an amino acid sequence set forth in SEQ ID NO:6;

(e) a polypeptide comprising an amino acid sequence set forth in SEQ ID NO:8;

(f) a polypeptide comprising an amino acid sequence set forth in SEQ ID NO:10;

(g) a polypeptide comprising an amino acid sequence set forth in SEQ ID NO:12;

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(h) a polypeptide having at least 90% identity to a polypeptide of any one of (a) and (c)-(g).

20. An antibody which is specific for a polypeptide of claim 19.

21. The antibody of claim 20 which is a polyclonal antibody.

5 22. The antibody of claim 20 which is a monoclonal antibody.

23. A method for diagnosing long QT syndrome in a person wherein said method comprises sequencing a KCNE2 polypeptide from said person or sequencing KCNE2 polypeptide synthesized from nucleic acid derived from said person wherein the presence a mutation described herein is indicative of long QT syndrome.

10 24. A method of amplifying an exon of KCNE2 wherein said method comprises using a pair of primers.

Sub A
25. A cell transfected with the DNA of claim 1.

Sub B
26. A cell transfected with the DNA of claim 2.

Sub C
27. A vector comprising the isolated DNA of claim 1.

Sub D
28. A vector comprising the isolated DNA of claim 2.

Sub E
29. A cell transfected with the vector of claim 27.

30. A cell transfected with the vector of claim 28.

31. A nonhuman, transgenic animal comprising the DNA of claim 1.

32. A nonhuman, transgenic animal comprising the DNA of claim 2.

33. A method to screen for drugs which are useful in treating a person with a mutation in *KCNE2*, wherein said method comprises:

- (a) placing a first set of cells expressing *KCNE2* with a mutation into a bathing solution to measure a first induced K^+ current;
- 5 (b) measuring said first induced K^+ current;
- (c) placing a second set of cells expressing wild-type *KCNE2* into a bathing solution to measure a second induced K^+ current;
- (d) measuring said second induced K^+ current;
- (e) adding a drug to the bathing solution of step (a);
- 10 (f) measuring a third induced K^+ current of cells in step (e); and
- (g) determining whether the third induced K^+ current is more similar to the second induced K^+ current than is the first induced K^+ current, wherein drugs resulting in a third induced K^+ current which is closer to the second induced K^+ current than is the first induced K^+ current are useful in treating said persons.

15 34. The method of claim 33 wherein said mutation is one described herein.

35. The method of claim 33 wherein said first set of cells, said second set of cells or both sets of cells are obtained from a transgenic animal.

36. The method of claim 33 wherein said first set of cells, said second set of cells or both sets of cells are transfected with human *HERG* RNA.

20 37. A method to screen for drugs which are useful in treating or preventing long QT syndrome, said method comprising:

- (a) placing cells expressing wild-type *HERG* and wild-type *KCNE2* into a bathing solution to measure current;
- (b) measuring an induced K^+ current in the cells of step (a);
- (c) placing cells expressing wild-type *HERG* and mutant *KCNE2* into a bathing solution to measure current;
- 25 (d) measuring an induced K^+ current in the cells of step (c);
- (e) adding a drug to the bathing solution of step (c);

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5 (f) measuring an induced K^+ current in the cells of step (g); and
(g) determining whether the drug resulted in an induced K^+ current more similar to or less similar to the induced K^+ current seen in cells expressing wild-type *HERG* and wild-type *KCNE2* as compared to the current seen in cells expressing wild-type *HERG* and mutant *KCNE2* in the absence of a drug,
wherein a drug which results in a current more similar to the current seen in cells expressing wild-type *HERG* and wild-type *KCNE2* is useful in treating or preventing long QT syndrome.

10 38. The method of claim 37 wherein said mutant *KCNE2* encodes one of the mutations described herein.

15 39. The method of claim 37 wherein: i) said cells of step (a) are cotransfected with wild-type *HERG* and wild-type *KCNE2*, ii) said cells of step (c) are cotransfected with wild-type *HERG* and mutant *KCNE2*, or iii) said cells of step (a) are cotransfected with wild-type *HERG* and wild-type *KCNE2* and said cells of step (c) are cotransfected with wild-type *HERG* and mutant *KCNE2*.

20 40. The method of claim 39 wherein: i) said cells of step (a), ii) said cells of step (c) or iii) said cells of steps (a) and (c) are transfected with RNA.

25 41. A method to screen for drugs which are useful in treating or preventing long QT syndrome, said method comprising:
(a) placing cells expressing wild-type *HERG* and wild-type *KCNE2* into a bathing solution to measure current;
(b) measuring an induced K^+ current in the cells of step (a);
(c) placing cells expressing mutant *HERG* and wild-type *KCNE2* into a bathing solution to measure current;
(d) measuring an induced K^+ current in the cells of step (c);
(e) adding a drug to the bathing solution of step (c);
(f) measuring an induced K^+ current in the cells of step (e); and

(g) determining whether the drug resulted in an induced K^+ current more similar to or less similar to the induced K^+ current seen in cells expressing wild-type *HERG* and wild-type *KCNE2* as compared to the current seen in cells expressing mutant *HERG* and wild-type *KCNE2* in the absence of a drug,

5 wherein a drug which results in a current more similar to the current seen in cells expressing wild-type *HERG* and wild-type *KCNE2* is useful in treating or preventing long QT syndrome.

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42. The method of claim 41 wherein: i) said cells of step (a) are cotransfected with wild-type *HERG* and wild-type *KCNE2*, ii) said cells of step (c) are cotransfected with mutant *HERG* and wild-type *KCNE2*, or iii) said cells of step (a) are cotransfected with wild-type *HERG* and wild-type *KCNE2* and said cells of step (c) are cotransfected with mutant *HERG* and wild-type *KCNE2*.

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43. The method of claim 41 wherein: i) said cells of step (a), ii) said cells of step (c) or iii) said cells of steps (a) and (c) are transfected with RNA.

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44. A method to screen for drugs which are useful in treating or preventing long QT syndrome, said method comprising:

- (a) preparing a transgenic animal cotransfected with wild-type *HERG* and wild-type *KCNE2*;
- (b) measuring an induced K^+ current in the transgenic animal of step (a);
- (c) preparing a transgenic animal cotransfected with wild-type *HERG* and mutant *KCNE2*;
- (d) measuring an induced K^+ current in the transgenic animal of step (c);
- (e) administering a drug to the transgenic animal of step (c);
- (f) measuring an induced K^+ current in the drug-treated animal of step (e);
- (g) determining whether the drug resulted in an induced K^+ current more similar to or less similar to the induced K^+ current seen in the transgenic animal cotransfected with wild-type *HERG* and wild-type *KCNE2* as compared to the current seen in a transgenic animal cotransfected with wild-type *HERG* and mutant *KCNE2* in the absence of a drug,

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wherein a drug which results in a current more similar to the current seen in transgenic animals cotransfected with wild-type *HERG* and wild-type *KCNE2* is useful in treating or preventing long QT syndrome.

45. The method of claim 44 wherein said mutant human *KCNE2* encodes a mutation disclosed herein.

46. A method to screen for drugs which are useful in treating or preventing long QT syndrome, said method comprising:

- (a) preparing a transgenic animal cotransfected with wild-type *HERG* and wild-type *KCNE2*;
- (b) measuring an induced K^+ current in the transgenic animal of step (a);
- (c) preparing a transgenic animal cotransfected with mutant *HERG* and wild-type *KCNE2*;
- (d) measuring an induced K^+ current in the transgenic animal of step (c);
- (e) administering a drug to the transgenic animal of step (c);
- (f) measuring an induced K^+ current in the drug-treated animal of step (e);
- (g) determining whether the drug resulted in an induced K^+ current more similar to or less similar to the induced K^+ current seen in the transgenic animal cotransfected with wild-type *HERG* and wild-type *KCNE2* as compared to the current seen in a transgenic animal cotransfected with mutant *HERG* and wild-type *KCNE2* in the absence of a drug, wherein a drug which results in a current more similar to the current seen in transgenic animals cotransfected with wild-type *HERG* and wild-type *KCNE2* is useful in treating or preventing long QT syndrome.

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47. A method for diagnosing a polymorphism which causes long QT syndrome comprising determining the *KCNE2* sequence in a patient by preparing cDNA from RNA taken from the patient and sequencing said cDNA to determine the presence or absence of mutations which cause long QT syndrome.

48. A method of assessing a risk in a human subject for long QT syndrome which comprises screening said subject for a mutation in a *KCNE2* gene by comparing the sequence of the

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KCNE2 gene or its expression products isolated from a tissue sample of said subject with a wild-type *KCNE2* gene or its expression products, wherein a mutation in the sequence of the subject is indicative of a risk for long QT syndrome.

49. The method of claim 48 wherein said expression product is selected from the group consisting of mRNA of the *KCNE2* gene and a *KCNE2* polypeptide encoded by the *KCNE1* gene.

50. The method of claim 48 wherein one or more of the following procedures is carried out:

- (a) observing shifts in electrophoretic mobility of single-stranded DNA from said sample on non-denaturing polyacrylamide gels;
- (b) hybridizing a *KCNE2* gene probe to genomic DNA isolated from said sample under conditions suitable for hybridization of said probe to said gene;
- (c) determining hybridization of an allele-specific probe to genomic DNA from said sample;
- (d) amplifying all or part of the *KCNE2* gene from said sample to produce an amplified sequence and sequencing the amplified sequence;
- (e) determining by nucleic acid amplification the presence of a specific *KCNE2* mutant allele in said sample;
- (f) molecularly cloning all or part of the *KCNE2* gene from said sample to produce a cloned sequence and sequencing the cloned sequence;
- (g) determining whether there is a mismatch between molecules (1) *KCNE2* gene genomic DNA or *KCNE2* mRNA isolated from said sample, and (2) a nucleic acid probe complementary to the human wild-type *KCNE2* gene DNA, when molecules (1) and (2) are hybridized to each other to form a duplex;
- (h) amplification of *KCNE2* gene sequences in said sample and hybridization of the amplified sequences to nucleic acid probes which comprise wild-type *KCNE2* gene sequences;
- (i) amplification of *KCNE2* gene sequences in said tissue and hybridization of the amplified sequences to nucleic acid probes which comprise mutant *KCNE2* gene sequences;
- (j) screening for a deletion mutation;
- (k) screening for a point mutation;

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5 a) placing cells expressing mutant *HERG* and wild-type *KCNE2* into a bathing solution to measure current;

b) measuring or detecting a first induced K^+ current in the cells of step (a);

c) adding a drug to the bathing solution of step (a);

d) measuring a second induced K^+ current in the cells of step (c); and

e) determining whether addition of said drug in step (c) inhibits, enhances, or alters the I_{Kr} by comparing said first induced K^+ current with said second induced K^+ current.

10 55. A method for determining the ability of a drug to affect the fast delayed rectifier potassium current (I_{Kr}), wherein said method comprises:

15 a) placing cells expressing wild-type *HERG* and mutant *KCNE2* into a bathing solution to measure current;

b) measuring or detecting a first induced K^+ current in the cells of step (a);

c) adding a drug to the bathing solution of step (a);

d) measuring a second induced K^+ current in the cells of step (c); and

e) determining whether addition of said drug in step (c) inhibits, enhances, or alters the I_{Kr} by comparing said first induced K^+ current with said second induced K^+ current.

20 56. The method of claim 55, wherein the *KCNE2* gene is selected from the group consisting of one of the following mutant *KCNE2* genes:

a) Gln 9->Glu (C 25 G);

b) Met 54->Thr (T 161 C);

c) Ile 57->Thr (T 170 C); and

d) Thr 8->Ala (A 22 G).

25 57. A method for determining the ability of a drug to affect the fast delayed rectifier potassium current (I_{Kr}), wherein said method comprises:

a) placing cells expressing mutant *HERG* and mutant *KCNE2* into a bathing solution to measure current;

b) measuring or detecting a first induced K^+ current in the cells of step (a);

c) adding a drug to the bathing solution of step (a);

d) measuring a second induced K^+ current in the cells of step (c); and

e) determining whether addition of said drug in step (c) inhibits, enhances, or alters the I_{Kr} by comparing said first induced K^+ current with said second induced K^+ current.

58. The method of claim 57, wherein the *KCNE2* gene is selected from the group consisting of one of the following mutant *KCNE2* genes:

- 5 a) Gln 9->Glu (C 25 G);
- b) Met 54->Thr (T 161 C);
- c) Ile 57->Thr (T 170 C); and
- d) Thr 8->Ala (A 22 G).

10 59. A method for determining a correlation between inheritance of a mutation in the *KCNE2* gene and reaction to a drug, wherein said method comprises:

- a) detecting a presence or absence of a mutation in the *KCNE2* gene in a patient;
- b) observing the reaction of said patient to an administered drug; and
- c) correlating said patient's genotype with said reaction.

15 60. A method as in claim 59, wherein said mutation is selected from the group consisting of:

- a) Gln 9->Glu (C 25 G);
- b) Met 54->Thr (T 161 C);
- c) Ile 57->Thr (T 170 C); and
- d) Thr 8->Ala (A 22 G).

20 61. A method for determining a correlation between inheritance of a mutation in the *KCNE3* gene and reaction to a drug, wherein said method comprises:

- a) detecting a presence or absence of a mutation in the *KCNE3* gene in a patient;
- b) observing the reaction of a patient to an administered drug; and
- c) correlating said patient's genotype with said reaction.

25 62. A method for determining a correlation between inheritance of a mutation in the *KCNE4* gene and reaction to a drug, wherein said method comprises:

- a) detecting a presence or absence of a mutation in the *KCNE4* gene in a patient;
- b) observing the reaction of a patient to an administered drug; and

c) correlating said patient's genotype with said reaction.

63. A mammal comprising a disruption in at least one allele of its endogenous *KCNE2* gene, wherein said disruption prevents transcription of messenger RNA from said allele of the *KCNE2* gene and results in a reduced level of *KCNE2* in said knockout mouse compared to a mouse without said disruption.

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64. A mammal comprising a disruption in at least one allele of its endogenous *KCNE3* gene, wherein said disruption prevents transcription of messenger RNA from said allele of the *KCNE3* gene and results in a reduced level of *KCNE3* in said knockout mouse compared to a mouse without said disruption.

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65. A mammal comprising a disruption in at least one allele of its endogenous *KCNE4* gene, wherein said disruption prevents transcription of messenger RNA from said allele of the *KCNE4* gene and results in a reduced level of *KCNE4* in said knockout mouse compared to a mouse without said disruption.

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66. A method of diagnosing long QT syndrome in a person, comprising:
(a) obtaining a nucleic acid sample from the person; and
(b) determining the identity of a base occupying a polymorphic site in a gene selected from the group consisting of human MiRP1, human MiRP2 and human MiRP3, the identity of the base indicating presence or absence of the syndrome, or susceptibility thereto.

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67. The method of claim 66, further comprising informing the person or a treating physician of the diagnosis.

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68. A method of identifying a polymorphic form correlated with long QT syndrome, comprising:

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(a) obtaining nucleic acid samples from a plurality of individuals characterized for presence or absence of long QT syndrome;

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(b) determining the identity of a base occupying a polymorphic site in a gene selected from the group consisting of human MiRP1, human MiRP2 and human MiRP3; and

(c) correlating identified bases with presence or absence of long QT syndrome in the individuals to identify a polymorphic form that correlates with long QT syndrome.

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